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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/895,840	06/28/2001	Catherine Guenther	R-409	4993

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 09/09/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/895,840	GUENTHER, CATHERINE	
	Examiner	Art Unit	
	Celine Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49* is/are pending in the application.

4a) Of the above claim(s) *16 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17-47 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-49 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I in Paper No. 12 is acknowledged.

Accordingly, claims 16 and 48 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1-15, 17-47 and 49 are currently under examination.

Claim Objections

Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim is drawn to a construct comprising a screening marker. Since it's unclear how it is different from the "selection marker," claim 2 fails to limit the subject matter of claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-15 and 44-47 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is a method of identifying an agent that modulates the RORγ gene expression and function by administering an agent to a RORγ gene knockout animal, and determine whether the expression or function of RORγ gene is modulated.

The guidance in the specification is limited in regarding this method. The specification does not teach a specific method in determining the expression or function of RORγ in a RORγ knockout animal. It is not known how to determine the expression or function of a gene that has already been knocked out. The prior art does not teach such a method either. In view of lack of guidance from both specification and prior art, one skilled in the art would have to engage in undue amount of experimentation to practice the method as claimed. If this aspect of rejection can be overcome, the scope of enablement rejection set forth below is applicable.

Claims 5-10, 17-43 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous knockout mouse comprising a disruption in the RORγ gene, wherein both alleles of the gene are inactivated, and exhibiting phenotypic features such increased spleen weight, thymic cortical expansion, medullary reduction, lack of lymph nodes, lymphoid infiltrates, or lymphoma as compared to wild type mice, and a method of producing such a transgenic mouse, does not reasonably provide enablement for other transgenic and/or knockout animals comprising any kind of disruption in RORγ gene. Further, the specification is not enabling for a knockout mouse comprising any disruption in RORγ gene and for any cell comprising any disruption in a RORγ gene. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 5-10, 17-43 and 49 are drawn to a cell comprising a disruption in a RORγ gene, a non-human transgenic animal comprising a disruption in a RORγ gene, a cell from that transgenic animal, a method of producing the mouse with any disruption in the said gene, and a method of identifying an agent having an effect on a phenotype associated with the transgenic mouse. Thus, the nature of the invention is directed to transgenic animals and methods of using the transgenic animals in identifying agents that modulate gene expression.

Breadth of Claims:

In the instant case, the claims 5-10, 17-43 and 49 encompass any transgenic animal containing any disrupted allele for the gene that encodes any RORγ. Further, the claims encompass any knockout mouse comprising any disruption in RORγ gene and exhibiting the phenotypes of a spleen abnormality, a kidney abnormality, and a liver abnormality as compared

to wild type mice. Further, the claims encompass any cell comprising any disruption in a RORγ gene and encompass all cells capable of undergoing homologous recombination (specification page 2, lines 1-3). The disruption, as disclosed in the specification (page 6, lines 26-31) includes any insertion, deletion or substitution in any portion of the gene (introns, exons, regulatory regions). The claims, therefore, encompass all such disruptions and also cover animals that exhibit enhanced RORγ activity (page 7, lines 1-2).

The specification does not provide an enabling disclosure for the full scope of transgenic animals of the type claimed. The only embodiment enabled by the specification within the scope of claims 5-10, 17-43 and 49 is for a homozygous knockout mouse comprising a disruption in the RORγ gene, that results in loss of function of the RORγ gene and exhibiting phenotypic features such as increased spleen weight, thymic cortical expansion, medullary reduction, lack of lymph nodes, lymphoid infiltrates, or lymphoma as compared to wild type mice, a method of producing such a transgenic mouse, and a method of identifying an agent that modulates the expression of RORγ gene and thereby ameliorates a phenotype associated with the disruption. Thus the breadth of claims is very broad and encompasses any transgenic animal and a knockout mouse with any disruption in any RORγ gene and includes any and all mutant forms, substitutions, deletions, or insertions in any RORγ gene (specification, page 6, lines 26-31). The claims also encompass phenotypes of said knockout mouse including increased kidney weight, liver weight and thymus weight which are not supported by the specification.

Amount of guidance in the specification and Working Examples:

The specification discloses the use of a specific RORγ gene in producing a homozygous transgenic knockout mouse, wherein the knockout mouse exhibits phenotypic changes that

include increased spleen weight, thymic cortical expansion, medullary reduction, lack of lymph nodes, lymphoid infiltrates, or lymphoma as compared to wild type mice.

The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a murine RORγ gene of wherein the disruption results in loss of function of the RORγ gene. The specification does not teach how to make and use the invention with other species of transgenic or knockout animals and with any knockout mouse with any form of disruption in the gene encoding RORγ, as claimed in the claims 5-10, 17-43 and 49. Further, the specification does not teach how to make and use any cell comprising any type of disruption in a RORγ gene as claimed. Moreover, according to Table 1, only the female knockout mouse but not the male knockout mouse exhibits a slight increase in liver, thymus and kidney weight. The specification also fails to disclose any other liver and kidney abnormality, and/or any kind of spleen, thymus, lymph nodes, lymphocytes, bone marrow and bone abnormality. The scope of claims 5-10, 17-43 and 49 thus surpasses that enabled by the specification.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the claims as specified and use the invention with any and all transgenic animals as claimed. The specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse containing two disrupted alleles for the gene that encodes a murine RORγ wherein the gene knocked out is a nonfunctional RORγ gene. However, neither the specification

nor the working examples provide enough guidance on how to practice the invention with any and all transgenic animals and/or transgenic mice carrying any and all transgene(s) of the types recited in the claims.

When considering the predictability of this invention, one has to remember that many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). The specification discloses the phenotype of a homozygous RORγ gene knockout mouse comprising a disruption in the RORγ gene and fails to disclose the phenotypes of any and all KO animals with a disruption in a RORγ gene. Thus, the phenotype of any transgenic or knockout animal is unpredictable. Thus, the specification, in the instant case, is not enabling for transgenic and/or knock out animals, including mice, that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification. Thus, the specification is enabling for a method of identifying an agent that modulates the phenotype of a KO mouse using only a homozygous KO mouse of the instant invention.

Further, the transgene expression and the physiological consequences of transgene products are not always accurately predicted in transgenic mouse studies (pg.62, paragraph1, lines 7-9 in Wall, R.J. 1996. Theriogenology 45:57-68). Thus, the invention while being enabled for a homozygous knockout mouse containing two disrupted alleles for the RORγ gene, does not extend the predictability of the invention to other animal systems.

The particular genetic elements required for expression varies from species to species. Our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (Wall, 1996). Therefore, the phenotype of knockout animals is not always predictable. For example, Jacks et al. (1992) describe Rb KO mice that do not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). Therefore, in the absence of specific guidance and working examples, the production of transgenic animals with the scope as claimed is unpredictable. In such a situation, one skilled in the art would not know how to make and use the invention as claimed, without undue experimentation.

The specification fails to provide an enabling disclosure for the preparation of other species of knockout animals besides mice having a disruption in the RORγ gene because the guidance offered in the specification is limited to the preparation of mice harboring such mutations and no teachings or guidance are offered in regard to how one would have prepared any other type of animal having the recited gene disruption. Since homologous recombination is required for gene targeting methods such as employed in the instant invention, embryonic stem (ES) cell technology must be available to carry out the method. The only species in which such technology was known was the mouse and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g. Bradley et al., paragraph bridging pages 537-538). Campbell and Wilmut, 1997 acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet there are no reports of any cell lines which contribute to the germ line

in any species other than the mouse (p. 65). Likewise, Mullins et al. (1996) teach that "[a]lthough to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated. This remains a major goal for the future and may well require the use of novel strategies which depart widely from the traditional methods used in the mouse" (p. S38, column 1, paragraph 1). Thus, knockout animals cannot be prepared for any species other than the mouse. Since ES cell technology was required to produce the claimed animals and practice the claimed methods of using such animals, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation to produce the claimed animals and to practice the claimed methods in species other than mice.

In view of the limited guidance in the specification, and limited working examples directed to transgenic, knockout mice with a specific knockout gene and exhibiting a specific phenotype, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to make and use the invention in its full scope as claimed. Thus, the enabled scope of the claims is limited to a knockout mouse comprising a homozygous disruption in the RORγ gene, wherein both alleles of the gene are inactivated, and exhibiting phenotypic features such as increased spleen weight, thymic cortical expansion, medullary reduction, lack of lymph nodes, lymphoid infiltrates, or lymphoma as compared to wild type mice, and a method of producing such a transgenic mouse.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 9, 10, 17-39, 41, 42 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 1-4 and 10, it is unclear how the target construct is arranged. In other words, is the first polynucleotide adjacent to the second polynucleotide or there is a selectable marker in between? Where is the screening marker located in the construct? In addition, it is also unclear whether the first and second polynucleotide is a contiguous sequence of the target gene or just portions of the target gene. Moreover, "selection marker," "screen marker" and "selectable marker" are not a gene or a piece of DNA, as such, they can't be part of a targeting construct.

Regarding claim 2, the term "screening marker" renders the claim indefinite because it is unclear what term encompasses. In other words, it is unclear how a "screening marker" differs from the "selection marker" recited in claim 1.

Regarding claims 9 and 41, the word "derived" renders the claim indefinite because the nature and number of derivative processes is unknown.

Regarding claims 17-39, 41, 42 and 46, the recitation of "a spleen abnormality, a kidney abnormality a spleen abnormality a liver abnormality" renders the claim indefinite because the "spleen abnormality" is repeated twice and there should be a comma in between each recited phenotype.

Claim 34 and 35 recites the limitation "abnormality lymphocytes" in line 1. There is insufficient antecedent basis for this limitation in the claim. The parent claim (17) only recites "abnormality in lymphocytes."

Claim 41 recites the limitation "transgenic mouse" in line 1. There is insufficient antecedent basis for this limitation in the claim. The parent claim (claim 40) is drawn to a method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour et al (1988, Nature, vol. 336, No. 24, 348-352), in view of Medvedev et al. (Genomics 1997, Vol 46, pages 93-102, AG).

The claims are drawn to a RORγ gene-targeting construct and a method of making said construct. The claims are further drawn to a cell comprising a disruption in a RORγ gene, and a method of producing a transgenic mouse comprising a disruption in the RORγ gene by homologous recombination using the target construct.

Mansour et al. teach a strategy for targeted disruption of the hprt gene and proto-oncogene int-2 in mouse embryonic stem cells and subsequent generation of knockout mice. Their teaching addresses the previous technical difficulty of obtaining embryonic stem cells carrying a non-selectable, targeted gene mutation at a locus of interest, and therefore provides a model which can be used to produce a homozygous mutation of any gene, regardless of its function, if a cloned fragment of the gene is available (see page 348, second paragraph, line 1-3,

third paragraph, line 1-5, and page 352, fourth paragraph, line 1-3). Mansour et al. further teach the generation of two targeting constructs, pRV9.1/TK and pINT-2-N/TK, each contains two sequences from an hprt gene and an int-2 gene respectively, and a neo selection marker gene in between the two sequences (see page 350, figure 3). However, Mansour et al. do not teach how to make a magnesium-dependent phosphatase gene targeting construct and knockout mouse.

Medvedev et al. teach that RORγ is induced during fat cell differentiation and expressed abundantly in T lymphocytes but not in B lymphocytes, suggesting a role in regulating both adipocyte function and specific T-cell functions (see page 101, lines 1-8). Medvedev et al. also teach that genetic alterations involving the human 1q21 region where the RORγ gene is located have been implicated in a variety of malignancies including lymphomas and renal carcinomas. Medvedev et al. suggest that further studies need to be done to determine whether genetic alterations in the RORγ gene are involved in these disease processes (page 101, lines 9-16). Medvedev et al. further teach the cloning of the mouse RORγ gene and provided the genomic sequence of this gene (see Figure 1).

Based on the teaching of Medvedev et al. that RORγ is involved in regulating both specific T cell and adipocyte function, it would have been obvious to one of ordinary skill in the art to knockout the RORγ to study its function. The ordinary artisan would have been motivated to knockout the expression of the RORγ gene because of its possible involvement in the disease process of lymphomas and renal carcinomas, as suggested by Medvedev et al. The ordinary artisan would have had reasonable expectation of success for making such a knockout mouse because of the teachings of Mansour et al., who teach a general method of targeted gene disruption in mice based on homologous recombination using a cloned fragment of a desired

gene, and Medvedev et al., who teach the coding sequence of the mouse RORγ gene. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Anne-marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER

Celine Qian, Ph.D.
September 9, 2002